

Listing of Claims:

1-88. (Canceled).

89. (Currently Amended) An in vitro composition of cultured embryonic stem cells comprising modified embryonic stem cells of an inbred strain of ~~animal~~ mice and one or more of: (i) unmodified embryonic stem cells of an inbred strain of ~~an animal~~ mice; (ii) progenies of the modified embryonic stem cells; and (iii) progenies of the unmodified embryonic stem cells, said modified embryonic stem cells each comprising at least one modification sequence, said composition being produced by a method comprising introducing a targeting DNA construct into a plurality of unmodified cells of an inbred strain of ~~animal~~ mice in vitro, wherein said targeting DNA construct comprises a targeting DNA sequence that is capable of homologous recombination with a non-selectable target DNA sequence in the genome of said plurality of unmodified embryonic stem cells, and wherein said targeting DNA sequence comprises: (i) said at least one modification sequence, and (ii) flanking sequences that are ~~derived~~ obtained from said inbred strain of animal.

90. (Currently Amended) The composition of claim 89, said method further comprises incubating said modified embryonic stem cells and one or more of: (i) said unmodified embryonic stem cells, (ii) progenies of the modified embryonic stem cells; and (iii) progenies of the unmodified embryonic stem cells, under conditions where said targeting DNA sequence undergoes homologous recombination with said target DNA sequence in the genome of said modified embryonic stem cells.

91. (Previously Presented) The composition of claim 90, wherein said targeting DNA construct is produced in a prokaryotic cell.

92. (Previously Presented) The composition of claim 91, wherein said prokaryote is *E. coli*.

93. (Currently Amended) The composition of claim 90 wherein 5% to 25% of said plurality of unmodified embryonic stem cells have taken up said targeting DNA construct and undergone homologous recombination between said target DNA sequence in the genome and said targeting DNA sequence.

94. (Currently Amended) The composition of claim 90 wherein 10% to 90% of said modified embryonic stem cells have undergone homologous recombination between said target DNA sequence in the genome and said targeting DNA sequence.
95. (Currently Amended) The composition of claim 90 wherein 30% to 50% of said modified embryonic stem cells have undergone homologous recombination between said target DNA sequence in the genome and said targeting DNA sequence.
96. (Canceled) The composition of claim 89 or 90, wherein said inbred strain of animal is a non-murine animal, a non-human animal, a mammal, or a vertebrate.
97. (Canceled) The composition of claim 89 or 90, wherein said inbred strain of animal is a mouse.
98. (Canceled) The composition of claim 89 or 90, wherein said modified cells are stem cells, germ cells, or somatic cells.
99. (Previously Withdrawn) The composition of claim 89 or 90, wherein said modified animal cell is a hematopoietic cell, a T-lymphocyte, an epithelial cell, an endothelial cell, an adrenal medulla cell, a keratinocyte, a fibroblast, an osteoblasts, an osteoclasts, a neuron, a ganglion cell, a retinal cell, a liver cell, a myoblast cell, or a cell of the Islets of Langerhans.
100. (Canceled) The composition of claim 89 or 90, wherein said modified cells are embryonic stem cells.
101. (Previously Presented) The composition of claim 89 or 90, wherein said target DNA sequence comprises a coding region, a promoter, an enhancer, a terminator, an intron, or an inter-genic region.
102. (Previously Presented) The composition of claim 89 or 90, wherein each of said flanking sequences is at least about 75, 100, 150, 200, 300, 500, 1,000, 2,500, 8,000 or 15,000 base pairs.
103. (Previously Presented) The composition of claim 89 or 90, wherein each of said flanking sequences is at least 97%, 99%, 99.5%, 99.6%, or 99.9% identical to said target DNA sequence.

104. (Previously Presented) The composition of claim 89 or 90, wherein said target DNA sequence and each of said flanking sequences comprises at least about 75, 150, or 500 base pairs in length that are 100% identical.

105. (Currently Amended) The composition of claim 89 or 90, wherein said targeting DNA sequence is ~~derived~~ obtained from cells of the same individual animal or a sibling thereof, as cells comprising said target DNA sequence.

106. (Previously Presented) The composition of claim 89 or 90, wherein said targeting DNA construct comprises a gene that is a selectable marker, an antibiotic resistance gene, a gene conferring the ability to grow on selected substrates, or a gene encoding proteins that produce detectable signals.

107. (Previously Presented) The composition of claim 106, wherein said gene is positioned in an intron in the targeting DNA.

108. (Currently Amended) The composition of claim 106 wherein said gene comprises a transcriptional start signal, a translational start signal, ~~and/or~~ a termination signal or a combination thereof.

109. (Previously Presented) The composition of claim 106 wherein said gene is a neomycin resistance gene, a hygromycin resistance gene, a thymidine kinase gene, a hypoxanthine phosphoribosyl transferase gene, or a guanine/xanthine phosphoribosyl transferase gene.

110. (Previously Presented) The composition of claim 108, wherein said transcriptional start signal comprises a metallothionein promoter, a thymidine kinase promoter, a beta-actin promoter, an immunoglobulin promoter, a SV40 promoter, or a human cytomegalovirus promoter.

111. (Previously Presented) The composition of claim 89 or 90, wherein said modification sequence comprises a gene that is a selectable marker, an antibiotic resistance gene, a gene conferring the ability to grow on selected substrates, or a gene encoding proteins that produce detectable signals.

112. (Currently Amended) The composition of claim 89, wherein said introducing step ~~comprises the use of~~ uses microinjection, electroporation, transfection, calcium phosphate precipitation, liposomes, viral capsids, protoplast fusion, or ballistic penetration.

113. (Currently Amended) The composition of claim 90, wherein said method further comprises selecting said modified embryonic stem cells and progenies thereof.

114. (Currently Amended) The composition of claim 90, wherein said target DNA sequence in said modified embryonic stem cells is modified by an insertion, a deletion, a substitution, or a combination thereof.

115. (Currently Amended) The composition of claim 89 or 90, wherein said at least one modification sequence is a sequence that is not present in the genome of said inbred strain of ~~animal~~ mice.

116. (Previously Presented) The composition of claim 114, wherein said deletion comprises a deletion of at least one exon, at least one intron, at least a non-coding region, or a combination thereof.

117. (Previously Presented) The composition of claim 90, wherein said at least one modification sequence disrupts or enhances expression of a coding sequence in said target DNA sequence.

118. (Previously Presented) The composition of claim 90, wherein said homologous recombination comprises a single crossover, a double crossover, or a gene conversion.

119. (Previously Presented) The composition of claim 90, wherein an allele of a gene in said target DNA has been modified.

120. (Previously Presented) The composition of claim 119, wherein the other allele of said gene has been modified.

121. (Currently Amended) The composition of claim 89 or 90, wherein said inbred strain of ~~animal~~ mice is 129 strain of mouse or BALB/c strain of mouse.

122. (Currently Amended) The composition of claim 89 or 90, wherein said plurality of unmodified embryonic stem cells are cells of a substrain of said inbred strain of ~~animal~~ mice.

123. (Currently Amended) The composition of claim 89 or 90, wherein said targeting DNA sequence is from a substrain of said inbred strain of ~~animal~~ mice.

124. (Currently Amended) The composition of claim 89 or 90, wherein said plurality of unmodified embryonic stem cells are ~~derived~~ obtained from a first substrain of said inbred

strain of ~~animal~~ mice and said targeting DNA sequence is from a second substrain of said inbred strain of ~~animal~~ mice.

125. (Currently Amended) The composition of claim 124 wherein said first substrain and said second substrain are the same substrain.

126. (Currently Amended) The composition of claim 89 or 90, wherein said at least one modification sequence comprises a nucleic acid that encodes a polypeptide and wherein said modified embryonic stem cells produce said polypeptide.

127. (Previously Presented) The composition of claim 90, wherein said at least one modification sequence corrects a defective gene in said target DNA.